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Title of Thesis: The Disposition of Topically Applied Agents

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THE DISPOSITION OF

TOPICALLY APPLIED AGENTS

by

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ABSTRACT

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The topical route of administration of drugs is usually employed for the treatment of skin disorders. However, some of these preparations can penetrate through the skin and exert systemic effects. The disposition of topically applied agents is being studied at both the basic research and the clinical level. The research is aimed at elucidating the processes of absorption into and metabolism by the skin as well as the disposition of these agents and/or their metabolites systemically. New, noninvasive drug delivery systems are being considered and developed to employ topical agents systemically under special circumstances.

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INTRODUCTION

At the present time there are three common routes of drug administration: intravenous, intramuscular, and oral. They have been the most widely studied and best characterized of dosage forms. Other methods of administration are used less frequently, usually under special circumstances. These alternate routes include inhalation, subcutaneous, sublingual, rectal, and topical administration. For example, topical agents like the corticosteroids are usually applied for a local effect, i.e., primarily to treat skin disorders (1). But topical agents have been noted to be able to penetrate through the skin and pass into the general circulation to produce systemic effects (2,3). These penetration and distribution processes in the skin are currently being studied, but yet the disposition of drugs applied to the skin is not completely understood.

PHARMACOKINETICS: BASIC CONCEPTS

Pharmacokinetics is the study of the time course of a drug and its metabolites in the body and the mathematical relationships used to describe it (4). "Model-dependent" pharmacokinetics involves the use of specific compartmental or physiological flow models of drug disposition. The drug and its metabolites are conceived to distribute into kinetically distinct spaces. Compartments need not correspond to real body spaces. In "model-independent" kinetics, numerical methods are used to arrive at pharmacokinetic parameters which do not depend on any specific model. A brief summary of the general concepts of pharmacokinetics that have been characterized for the intravenous, intramuscular, and oral routes of administration will be presented as a reference for comparison with the topical dosage form.

The pharmacokinetic parameters of bioavailability, distribution volume, and clearance quantitatively characterize the body's dispositional responses to a drug. By definition, intravenous administration implies instantaneous release of a drug into the bloodstream. Any other dosage form requires some absorption process in order to reach the systemic circulation. The "bioavailability" of a dosage form refers to the rate and extent of this absorption as compared to an intravenous dose. The extent of bioavailability, designated as F, is usually expressed as a fraction ranging from 0 to 1, with 1 being the reference value for the intravenous dose. One method of estimating F is to estimate the area under the plasma concentration vs. time curve (AUC) for both the oral (or topical, inhaled, sublingual, or intramuscular) dose and for the intravenous dose and comparing them as follows, with a correction for dosage sizes:

$$F = \frac{AUC_{oral}}{Dose_{oral}} \Big/ \frac{AUC_{IV}}{Dose_{IV}}$$

The percent bioavailability (%F) is calculated as %F=Fx 100. A model-independent AUC is estimated by a numerical method such as the trapezoidal rule. Although the rate of bioavialability may be estimated as a model-dependent zero or first order absorption rate process, a model-independent approach may be applied using statistical moments (5). Here, the absorption time rather than the rate of absorption is determined. To do this, the first moment or mean residence time (MRT) of the drug in the system for both doses is calculated by numerical integration:

$$MRT = \int_0^\infty tC_p\,dt \Big/ \int_0^\infty C_p\,dt$$ where t=sampling time
C_p=plasma concentration of drug at time t

Subtracting the value of the MRT of the standard dose (IV dose) from the MRT of the test dose (oral or other) gives the mean absorption time for that specific drug and method of administration.

Distribution is the dispersion of a drug into the tissues of the body (6). The distribution phase of a plasma concentration vs. time curve is seen early after intravenous bolus administration as a drop in plasma level that is more rapid than that observed in the terminal elimination phase. It is characterized in model-dependent kinetics as a first-order transfer between compartments. Distribution depends on the molecular weight, lipid solubility, pK, and protein binding affinity of the drug. The apparent volume of distribution (V_D) for a drug is a parameter which relates the plasma drug concentration to the total amount of drug in the body. This volume term usually does not correspond to a real physiologic space, but can parallel body spaces in size like total body water. A distribution space greater in size than total body water implies that there is strong binding of drug in body tissue(s).

Disappearance of a drug from the plasma is described by the pharmacokinetic parameters of half-life and clearance. Often the drug is metabolized prior to excretion, and this biotransformation can be included in a compartmental model.

The half-life ($t_{\frac{1}{2}}$) of a drug is a measure of the survival time in plasma or tissue. It is calculated as $t_{\frac{1}{2}}=\ln(2)/K_e$, where K_e is the first order elimination rate constant of the drug in a single compartment system. This K_e term may be a composite sum of first order excretion and biotransformation processes. If a single compartment model does not fit the plasma concentration-time data, then the elimination half-life is obtained from the final elimination phase slope of the curve. In this case, the final linear portion of the log plasma concentration vs. time plot is assumed to be a result of the irreversible elimination from the system, and is not related to any distribution process.

The concept of clearance refers to the removal of drug or metabolites from the plasma, tissue, compartment, or body. It is calculated as $CL=K_e V_D$, where K_e is the elimination rate constant and V_D is the distribution space. Clearance is defined as the volume of fluid from which the drug is removed per unit time. Common units for clearance are ml/min or other volume/time units. Clearance gives a measure of elimination rate as does half-life, but the clearance term gives more information about the process. It involves the distribution space term, so changes in this parameter arising fron a disease state will alter the clearance, but the half-life may remain unchanged. A measure of the half-life alone may not reflect a change in the body's handling of the drug where the clearance term makes it apparent.

DRUG MOBILITY THROUGH THE SKIN

A drug applied topically, whether for local or systemic use, may permeate into or penetrate through the skin. Intact skin is a fairly good barrier against foreign substances, but it is not totally impermeable. Transport processes have been noted in both directions across the skin (7,8).

I. Anatomy (see figures 1-4)

The skin has three distinct layers: the epidermis, the dermis, and the subcutaneous fat (9). The principal barrier region of the skin is thought to be the stratum corneum, the uppermost layer of the epidermis. The stratum corneum is heavily keratinized; it is up to 10 cell layers thick. The cells in any layer have significant overlap with adjacent cells. The water content associated with these cells depends on the temperature and relative humidity surrounding the skin's surface (10).

Beneath the stratum corneum lies the epidermis and the dermis. The microcirculation is located within the dermis, 100μ below the skin surface (11). Drugs that reach the microcirculation are transported to the general circulation. Interspersed along the skin are sweat glands and hair follicles. These skin appendages are also possible sites of drug penetration, through shunt pathways.

The stratum corneum appears to be the limiting barrier to drug passage through the skin. Studies by Marzulli (12) demonstrated that the stratum corneum is the least permeable part of the epidermis. Excised skin from cadavers or surgical biopsies was prepared and mounted on diffusion cells. All skin samples were used less than 12 hours post

excision. Epidermis was separated from the dermis by a heat separation process. Epidermis, dermis, full thickness skin, and dissected stratum corneum preparations were tested. Stratum corneum samples were also prepared by stripping forearm skin of volunteers with cellophane tape and recovering the skin from the tape. A ^{32}P-labelled organophosphate liquid was applied to the surface of each diffusion cell, and a 38^{o} isotonic saline solution was washed under each cell to collect the penetrating radioactivity. The saline solutions were counted, and effluent penetration rates were calculated. The slowest penetration rate was reported in the stratum corneum, followed closely by the epidermis. Full thickness skin had the next higher penetration rate, then dermis. The skin preparation with the stratum stripped away had a penetration rate that was a bit slower than dermis. The author concluded that the stratum corneum is the least permeable skin component tested. The experiments of different skin components were done in parallel with skin from adjacent areas to lessen the chance of encountering regional differences in skin thickness from samples taken from different areas. The author also commented that these in vitro studies were of excised skin, and no firm conclusions could be made of live in vivo transport processes.

The stratum corneum acts as a passive but not inert diffusion barrier. If the stratum corneum is stripped off, the skin can be a hundredfold more permeable (13). From a personal survey of the literature on the subject of skin penetration to the present, no active transport processes across the skin have been reported.

II. Diffusion Pathways

The passage of materials through the stratum corneum may be intercellular, transcellular, or through shunt pathways such as the

hair follicles and sweat glands. Since there is overlapping of adjacent keratinized cells in each layer of the stratum corneum, intercellular passage seems unlikely as a major route (14). Shunt diffusion has been documented in percutaneous absorption studies, especially early in the time frame of the exposure period. An abstract by Shelley and Melton reported that application of 10% histamine in propylene glycol produced perifollicular wheals which later became confluent. Application of an epinephrine solution produced immediate perifollicular skin blanching which also became confluent with the rest of the skin surface (15). When the authors changed application site for the agents, they noticed the greatest immediate results in the hairy parts of the body. Yet the total surface area of these shunts is very small compared to the total skin surface area, about 0.1% of the total. Shunt diffusion is an event which is significant soon after application of the agent. However,the bulk flow of substance across the skin seems to be transcellular, through the intact cells of the stratum corneum (16).

III. Steady State Diffusion: Fick's First Law

Passive diffusion is the only mechanism for percutaneous transfer for most compounds. Diffusion rates are dependent upon the concentration gradient across the skin as well as the physico-chemical properties of the solute, the vehicle, and the skin.

Diffusion is a transfer process due to random molecular collisions. Overall, it can be viewed as an equilibrium process, where steady state is achieved when the forwards and reverse transfer rates are equal. Fick's first law of steady state diffusion can be applied

to the transfer of drug through the stratum corneum. This law states that the amount of solute (Q) diffusing across unit area (A) per unit time (t) is proportional to the concentration gradient (ΔC), and is called the solute flux (J) (17).

Eq. 1. $$J=\frac{Q}{A\,t}=\frac{D\Delta C}{\delta}$$

where D=diffusion coefficient (cm^2-sec^{-1})

δ=membrane thickness (cm)

This transfer process is first order, with the transfer rate depending on the concentration of solute delivered to the skin.

Since the skin is not inert and may interact with the solute, Eq. 1 may be expanded to include other factors:

Eq. 2. $$J=\frac{K_m D\Delta C}{\delta}=K_p C_v$$

Where K_m =the solvent-membrane distribution coefficient: $\frac{\text{solute per cc tissue}}{\text{solute per cc solvent}}$

C_v =concentration of solute in vehicle

K_p = permeability constant ($cm\text{-}hr^{-1}$)

Each componentof Eq. 2 is a variable affecting the rate of solute transfer across the skin and will be discussed in some detail.

1. Diffusion Coefficient-Permeability Constant

The diffusion coefficient of the solute in the stratum corneum is a measure of the permeability of the stratum corneum. If the solute particles are assumed to be spherical and the solvent particles are the same size or smaller, then the diffusion coefficient can be related to the Stokes-Einstein equation(18):

Eq. 3. $$D=kT/6\eta r$$

Where k=Boltzmann constant
T=absolute temperature
η=viscosity of the stratum corneum
r=hydrodynamic radius of the drug

According to Eq. 3, the larger the radius of the drug, the smaller the diffusion coefficient and the slower the rate of permeability. In a series of N-alcohols increasing in size from methanol to octanol, the larger sized molecules had decreased diffusion potentials (19).

But the permeability constant (20) is a combined term, $K_p = DK_m/\delta$ involving the skin thickness δ and the solvent/membrane partition coefficient K_m as well as the diffusion coefficient. In the same series of alcohols, the permeability constant rises 150-fold from methanol to octanol despite the slight decrease in the diffusion coefficient because of the overwhelming influence of the solubility partition coefficient K_m. The increased lipophilicity of octanol in stratum corneum relative to that of methanol increases the permeability much more than the change in diffusion coefficient decreases the diffusion potential.

2. Solute/Membrane Partition Coefficient

The partition of the drug in the vehicle vs. the stratum corneum is the dominant physiologically relevant factor, but is not always the one measured. Usually, the partition coefficient measured is an oil/water partition where the oil is octanol or olive oil. The increased oil/water partition coefficient in a series of alcohols of increasing size correlates to increased permeability in the stratum corneum (21) by virtue of increased lipophilicity.

3. Concentration Gradient

Since the flux of solute through the skin is directly proportional to the concentration gradient, increasing the amount of solute applied should increase its permeation. However, once the solute is dissolved in the stratum corneum, it is possible for it to diffuse out of the skin back into the vehicle. If the concentration

difference across the skin is large enough, there should be virtually no significant amount of back diffusion of the drug out of the body.

4. Vehicle Effects

The drug applied topically is usually delivered in solution or suspension in some solvent or vehicle. The drug must be released from the vehicle and taken up by the stratum corneum. The rate limiting step in permeation into the stratum corneum may be the transfer from vehicle to stratum corneum (22). This transfer is slower than the transfer of drug through the epidermis, or from epidermis to the vascular bed.

Hydration

The majority of topically applied drugs are applied in aqueous solutions or water miscible vehicles.
Regardless of the nature of the vehicle, the stratum is a tissue that contains its own endogenous water, which implies that the drug must dissolve into and/or diffuse through water (23). The agent may dissolve in this tissue water and transfer through the cells. The penetration of water soluble molecules through the skin depends on the water surrounding the solute. Hydration of the skin increases the *in vivo* penetration rates of nonelectrolytes (24). In a study of ^{14}C-labelled caffeine penetration rates through the skin by Zesch (25), four vehicle formulations were tested: vaseline, woolwax, polyethylene glycol, and a hydrophilic aqueous ointment. The radioactivity recovered was calculated to determine permeability of the agent to the skin preparation in a diffusion cell for each of the vehicles. The calculation of amount of agent penetrating through the skin by this detection method is actually an estimate of how much caffeine or labelled metabolite passes through the skin, if the skin can transform caffeine.

The author reported that the fastest penetration of the radioactive label was afforded by the hydrophilic ointment which apparently aids permeation by increasing the hydrated state of the stratum corneum.

The use of an occlusive vehicle such as an oil/water emulsion or using an occlusive film such as saran wrap can increase drug delivery. Occlusion of the skin probably results in increased hydration of the stratum corneum at the application site by trapping the endogenous tissue water through prevention of evaporation. Stoughton and McKenzie (26) reported that occlusion increased the penetration of corticosteroids into the skin 100-fold.

Drug Release From Vehicle

In order to reach the stratum corneum, the agent must be released from its vehicle. Only the drug dissolved in the skin is available for diffusion, so it must partition from the vehicle to the stratum corneum (27). The concentration of diffusable drug is optimized by assuring that all drug is initially solubilized in the vehicle. If the drug precipitates out of the vehicle, it may not be available to enter the skin. If the water evaporates from an emulsion, the hydrophilic drug may have to travel through oil before it reaches the surface of the stratum corneum.

Blank and Scheuplein (28) have postulated that the release of drug is favored from a vehicle with a low affinity for the drug. For example, ethanol penetrates better into skin from oil than water, but heptanol is released better from an aqueous medium. The drug should be soluble in its vehicle, but not so soluble that it cannot be released well into the stratum corneum.

Penetration Enhancers

Vehicles or components of vehicle solutions known as penetration enhancers increase the permeability of stratum corneum to solutes. They are usually organic liquids, and some work by chemical insult to the skin, i.e., they damage the penetration barriers of the skin (29). Penetration enhancers can be divided into two groups: the organic solvents and the fatty alcohols. The organic solvents include acetone, ethanol, propylene glycol, and dimethyl sulfoxide (DMSO). The fatty acids, esters, and alcohols can be considered as surfactants which change the surface properties of the skin and can wet the stratum corneum more effectively. If the skin is hydrated better, it is likely to have increased permeability to drugs.

The organic solvents like acetone and ethanol may actually injure the stratum corneum to afford increased permeability. These solvents can extract lipids *in vitro* and may remove the lipids from the skin surface. DMSO and other aprotic solvents appear to pass through the stratum corneum. DMSO forms strong hydrogen bonds to water molecules (30). It has been proposed that DMSO binds to tissue water and displaces it, resulting in a looser structure and increased permeability.

DMSO works as a penetration enhancer in concentrations of 80% or higher, and these concentrations have been found to change the ultrastructure of the skin. Montes et. al. (31) applied solutions of 90% DMSO topically to shaved guinea pigs. Skin biopsies were removed and fixed for electron microscopy. The keratin patterns of the stratum corneum were found to be irregular in the DMSO treated samples and keratin was found in deeper skin layers that is not present in the control samples. Plasma membranes and fibrils in the treated samples were swollen and disrupted. If DMSO changes the structure of the skin,

it is reasonable to conceive that there is a possibility of some systemic effect resulting from repeated dosage with DMSO.

5. Skin Condition and Thickness

If there is any change in the barrier layer of the skin, there is increased permeability to solutes. If the stratum corneum is damaged due to cuts, lesions, or other pathology, the barrier is weakened and permeability rises. If the stratum corneum is removed by strippings with cellophane tape, the skin has lost part of its protection against foreign substances.

Skin thickness is another factor in Fick's diffusion equation. If the stratum corneum is thicker in some areas than others, permeability should decrease in the thicker skin due to the longer distance through which the solute must travel. The body in fact is not uniform in skin thickness, and there are regional variations in permeability to drugs. Feldman and Maibach (32,33) studied penetration of labelled corticosteroids and pesticides in vivo on human skin. They applied the drugs dissolved in acetone to several sites on the body. They measured total radioactivity excreted in the urine as an index of systemic absorption. Measuring urinary excretion of a labelled compound tells how much label entered the body, but does not distinguish between the agent applied and its metabolites. They found that the most permeable regions of the skin under the experimental conditions were the scrotal skin, and the plantar and palmar surfaces of the foot and hand. Scheuplein (34) explains the increased permeability of the soles and palms by noting that these callous pads have a high diffusivity. A general order of permeability by body region to simple small molecules (in descending order) is as follows: plantar, palmar, dorsum of the hand, scrotal and scalp skin behind the ear, axillary skin, followed by

scalp, arms, legs, and trunk.

6. Reservoir Effect

The stratum corneum has been presented so far as a barrier to penetration of xenobiotics into the general circulation. It has been considered to be a primarily lipophilic barrier containing some endogenous water into which aqueous solutions may pass. But this region of the skin may also act as a reservoir to topically applied substances, where they may reside temporarily and release slowly and continuously, in a fashion similar to infusions or depot preparations.

Evidence supporting the reservoir phenomenon in the stratum corneum was presented by Vickers (35). He applied fluocinolone cream to forearm skin of humans and occluded it with plastic wrap for 16 hours to increase penetration. He found that occlusion of the same site 2 days later without repeated dosage still resulted in the same local vasoconstrictor response to the steroid that was originally used to monitor the permeability to the initial dose. Occlusion every other day resulted in a vasoconstrictor response in the patients for 3 to 15 days, demonstrating that the drug was still resident in the skin. Patients who received intradermal steroid injection responded with local vasoconstriction which did not reappear 2 days later. Those patients whose stratum corneum was stripped by cellophane tape were also given topical steroid. Intense vasoconstriction was the immediate response, but upon later occlusion showed no further response. Intact skin that was treated by the topical agent and then stripped by tape the day following the dosage showed no further vasoconstriction to later occlusion. All of the evidence presented point to the presence of a reservoir site in the skin which resides in the stratum corneum.

SYSTEMIC KINETICS

If not metabolized during transience through the skin (see the following section), the drug passes through the skin and enters the microcirculation, and becomes available to the general circulation. When the drug reaches the bloodstream, its pharmacokinetic and pharmacodynamic properties (i.e., V_D, clearance, metabolism, elimination, mechanism of action) are identical to the same drug administered by any other method (36).

The extent of bioavailability of a topically applied agent is estimated by comparison to a standard dosage form, typically an intravenous dose. A study performed by Wester and Noonan (37) compared the IV and topical dosages of a ^{14}C-labelled steroid in Rhesus monkeys (see Table I and Figures 5-7). The topical drug was applied in an acetone solution and was left unoccluded for 24 hours. Cumulative urine and fecal excretion of radioactivity was collected and calculated for both dosages. Blood samples were drawn periodically for 4 weeks. The average plasma concentration of drug for the group of subjects was plotted vs. time for the IV and the topical doses. The AUC was estimated for each curve, and an extent of bioavialability was calculated as 0.49%. Since the monkeys' skin surfaces were washed after 24 hours, it is uncertain how much of the topical dose was washed away. Consequently, the bio-availability calculation which was based on the assumption that the entire dose was delivered is really an estimate of the absorption of an unknown fraction of the dose.

Sometimes a comparison is made of topical administration with a commonly employed route of administration other than the intravenous.

For example, organic nitrates that are used to treat angina pectoris have a high hepatic extraction ratio (38). These drugs are routinely administered sublingually to reduce the first-pass metabolism by the liver that is commonly encountered in oral doses, and yet allow rapid entry into the bloodstream for quick relief of pain. Mansel-Jones and coworkers (39) compared the plasma concentrations of isosorbide dinitrate administered sublingually and topically to humans. The topical dose was a weighed sample of a commercial ointment applied without occlusion for 12 hours to a measured surface area of the subjects' chests. The authors reported that the ointment delivered a lower peak blood level at a later time than the sublingual dose, and sustained this low level for a longer time (see Tables II-III and Figure 8). The slower rise in plasma level from the topical dose is consistent with the longer absorption time necessary for the drug to pass through the skin rather than through the mucosal lining of the mouth in the sublingual dose. Since the topical dose is a continuous release rather than the single dose tablet, a longer lifetime of drug in plasma would be expected. Again, the topical dose in this study was washed off the skin after 12 hours, so the entire dose was probably not delivered to the subject. The authors' estimate of the extent of bioavailability of the topical dose compared to the sublingual was reported as 30%. This estimate is again only an estimate of an undetermined fraction of the topical dose. If the amount of drug wiped away could somehow been measured, a more accurate estimate of the bioavailability for this exposure period could have been calculated.

LOCAL METABOLISM BY THE SKIN

If the topically applied agent reaches the bloodstream, its disposition is the same as if it entered by any other route. However, the skin itself is not merely an inert diffusion barrier. It is a metabolically active tissue capable of biotransforming foreign and endogenous substances. The metabolic activity of the skin may substantially contribute to the sum of the metabolic routes in the body (40). There are active enzymes in the epidermis as well as in the dermis. They include those for the synthesis and breakdown of protein, carbohydrate, and lipid.

Steroid metabolism in the skin has been shown to be stereo-specific at the C-5 position, where only 5-α insertions of hydrogen are made in the skin, while the liver substitutes 5-α and 5-β hydrogens equally as well (41).

Carcinogens can be activated on the skin. Animal skin is commonly used for tumor induction testing. Repeated applications of polyaromatic hydrocarbons to mouse skin resulted in neoplasm formation (42). The metabolites of the hydrocarbons induce the tumors. The hydrocarbons are biotransformed to active carcinogens by several enzymic reactions, including one involving aryl hydrocarbon hydroxylase (AHH). Akin and Norred (43) treated mice with topical benzanthracene 24 hours prior to sacrifice. The skin was shaved, excised, and rinsed with cold saline. The epidermis was scraped away with a scapel blade. Then the preparations were homogenized and assayed for AHH activity by fluorimetrically measuring the conversion of benzpyrene to 3-hydroxy benzpyrene. The authors reported that AHH activity is

unequally distributed in the skin, with the epidermis being more active than the dermis.

Extensive study of the metabolism of steroids by the skin has been done by Hsia and coworkers. They used in vitro preparations of human foreskin, skin biopsies from surgical incision sites, and cadaver skin. The skin used was sliced and incubated in Krebs-Ringers Phosphate buffers with ^{14}C-labelled steroids. The metabolites were separated and identified chromatographically. In a 1965 study (44) it was noted that cadaver skin had a low activity in transforming hydrocortisone to cortisol. Adding NADPH and NADH to the incubation media restored this metabolic activity comparable to living skin. The authors postulated that cadaver skin was depleted of these cofactors. They also incubated a scraped epidermis preparation from foot sole skin (which has no sweat glands or hair follicles) to demonstrate that the metabolism detected is primarily carried out by the skin cells and not by shunt pathways. In a 1966 report (45) of the biotransformation of ^{14}C cortisol by skin slices, several metabolites were deteced including cortisone. Both the epidermis and the dermis separately were found capable of metabolizing cortisol. They reported in 1967 (46) that the biotransformation of cortisone to cortisol also occurs in the viable cutaneous tissue.

RESEARCH DIRECTIONS

Current research involving the use of topical agents appears to be aimed several ways. A primary interest is in increasing our understanding of the barrier function of the skin, especially with regards to transport processes and metabolic activity. Some researchers are postulating mathematical and schematic models to describe these processes. For example, Cooper (47) is developing models to estimate in vivo skin permeability coefficients, and Ayres and Lîndstrom (48) are working on theoretical models for drug release from suspensions into the skin. Others are taking the available information and applying it to improve topical drug therapy. Recently a new drug delivery system has been developed to noninvasively carry a drug through the skin for systemic use (49), which will be discussed in detail below.

I. Formal Models of Drug Disposition by Skin

The work of Higuchi et.al. involved the use of diffusion cells and whole epidermis to test a model system where the skin is assumed to both transport and metabolize the drug simultaneously (50). They considered the skin as a 2-ply laminate of stratum corneun and vaible epidermis. The epidermis was simplified to be a homogeneous membrane with respect to enzyme activity which was also acting as a perfect diffusion sink for the drug. The stratum corneum was assumed to be the principal diffusional resistance. Both the inside and the outside of the skin were assumed to be well-stirred homogeneous systems.

Their work at present is a model that puts to practical use the concepts of simultaneous transport and metabolism by the skin to enable a prodrug to be activated as it enters the body (51). They are evaluating a physical prodrug delivery model for vidarabine

(9-β-D-arabinofuranosyladenine). The drug is applied to intact hairless mouse skin as viderabine-5-valerate, which is more permeable in the skin. The valerate is converted in the stratum corneum to viderabine, the active drug (see Figure 9). The esterase necessary for the conversion is resident in the skin, as well as a deaminase that metabolizes vidarabine. Originally the activity for both enzymes was assumed to be homogeneously distributed in the skin, but it was experimentally determined that the esterase has higher activity in the upper epidermis, while the deaminase has higher activity in the dermis. In summary, the metabolic activity of the skin should not be overlooked in any drug delivery system,and may be put to use with prodrugs when the therapeutically active compound is difficult to deliver to the system.

II. The Status of Topical Drug Therapy

A review by Maibach (52) on the percutaneuos penetration of corticosteroids outlines some of the research areas in the field that need to be further investigated in order to improve topical drug therapy. These areas presented can be adapted to discuss the status of topical therapy in general.

1. Vehicles

Vehicle formulations are necessary to deliver the drug to the skin surface. If the solute is sparingly soluble in the vehicle, it will be more easily released into the stratum corneum. Research to improve the nature of the vehicle to enhance permeability would reduce the need for occlusion. The solubilizers used in the vehicle should be optimized in order to give a maximum permeability of the agent while minimizing damage to the skin.

2. Wastage

Presently a large fraction of a drug applied topically may be

washed away. As well as developing vehicles to improve delivery, research should be directed to understand the nature and kinetics of the absorption process. Once it is known how long it takes for the drug to reach the target tissue, patient instructions can be clarified so that the preparation can be used effectively.

3. Cutaneous Metabolism

It is still unknown what happens to many topically applied agents in the skin. The idea of a first-pass metabolism in the skin will surely be studied further to characterize it, and to determine if skin metabolism parallels that of the liver. Differences in the metabolic activity of diseased skin is another research problem that will likely be out of use in the future planning of topical drug regimens.

THERAPEUTIC IMPLICATIONS

Once the drug disposition in the skin is better understood, therapeutic advances may follow. The state of the art of topical therapeutics is still primitive and mostly experimental, but new drug delivery systems utilizing topical administration may be more widely marketed in the future. An example of a topical drug delivery system in use now is that of Shaw et.al. (53). This system passes scopolomine, an anti-motion sickness agent through intact skin into the bloodstream. The delivery system is called the Transepidermal Transport System (TTS) (see Figure 10). The scopolomine is applied as a priming dose in a gel adhesive as well as in a continuous dose from a matrix in a disc on top of the gel, which are both enclosed in an occlusive patch. The small patch is placed behind the ear of the subject, where it is of little annoyance. It is also conveniently in an area of the body where the stratum corneum is known to be permeable to scopolomine. The drug is released noninvasively at low continuous levels to the bloodstream. In a human crossover study (54), scopolomine was administered by an IV infusion of 3.7-6.0 µg/hr to 6 subjects for 72 hours and by TTS (.5mg/ 3 days). Urine was collected over the period every 12 hours and assayed. The authors reported that at steady state (24-72 hours) there was no significant difference in excretion rate of the drug between administration routes. Early after administration (0-24 hours) higher excretion rates were found in the TTS group. The authors felt that the scoplomine may be stored in the skin. They concluded that at steady state, the TTS is functionally equivalent to an IV infusion with respect to rate and duration of input. Clinical trials (55,56) vs. placebo and oral dimenhydrate found the TTS significant in preventing

simulated motion sickness.

Other drugs may be suited for TTS-like delivery systems. The drug and vehicle must be non-toxic to the skin. Agents used to treat a chronic condition could be adapted to this method of administration, changing drug regimens to decrease the need for oral or injected doses. Even if a loading dose is administered intravenously or orally, if the maintenence dose could be delivered transdermally then patient compliance may increase, since the transdermal dose is noninvasive and continuous. Drugs with a narrow therapeutic index could be administered transdermally at a controlled continuous rate, similar to an infusion. As the technology develops and the disposition of topical agents is better understood, new drug delivery systems may be evaluated as therapeutic alternatives.

Time, *Hours*	Plasma Concentration[a] *ng/ml*	Time, *Hours*	Plasma Concentration,[a] *pg/ml*
0.08	252	1	37
0.17	171	2	33
0.25	117	3	40
0.5	75	4	36
1	50	6	36
2	39	8	40
3	40	24	67
4	35	27	44
6	32	48[b]	63
8	34	72	72
10	27	96	58
24	17	120[b]	79
48	15	144	67
80	12	168	79
96	9.3	192	69
120	9.3	216	77
144	7.9	240	76
168	6.6	312	85
192	6.1	480	54
217	5.5	576	25
289	4.0		
336	3.2		
576[c]	1.2		
696	0.81		

[a] Each value is the mean for 3 monkeys. Values are calculated as ng/ml or pg/ml equivalents of radioactivity assuming the same molecular weight as SC-23110.

[b] Mean of 2 monkeys.

[c] Calculated from linear regression line.

Table I

Plasma radioactivity following intravenous (0.48 mg) or topical (1.0 mg) administration of ^{14}C-SC-23110 to Rhesus monkeys. (adapted from Wester and Noonan)

Mean Plasma Isosorbide Dinitrate Concentrations After Sublingual Administration of a Tablet Containing 5 mg and After Application of an Ointment (Actual Mean Dose 77.5 mg) to the Skin

Time	Mean plasma isosorbide dinitrate (ng/ml)*	
	Sublingual	Ointment
5 min	2.8 ± 2.2	—
7.5 min	5.7 ± 3.9	—
10 min	10.5 ± 7.8	—
12.5 min	13.2 ± 8.3	—
15 min	12.6 ± 6.8	—
17.5 min	14.8 ± 7.9	—
20 min	15.1 ± 7.3	—
30 min	15.9 ± 7.0	1.4 ± 2.7
45 min	8.2 ± 2.6	1.3 ± 0.9
1 hr	6.2 ± 1.7	1.1 ± 0.8
1.5 hr	4.5 ± 2.9	2.1 ± 1.7
2 hr	3.2 ± 2.8	3.5 ± 3.7
3 hr	—	1.6 ± 1.6
4 hr	—	3.3 ± 2.5
6 hr	—	6.2 ± 3.9
8 hr	—	3.7 ± 4.1
12 hr	—	2.9 ± 3.0
24 hr	—	1.2 ± 1.0
28 hr	—	0.9 ± 0.5
32 hr	—	1.0 ± 0.8

Table II

Plasma concentrations of Isosorbide Dinitrate measured by Gas Chromatography after extraction for sublingual and topical dosages. The * denotes that the plasma levels are reported with their standard deviations. (adapted form Mansel-Jones et. al.)

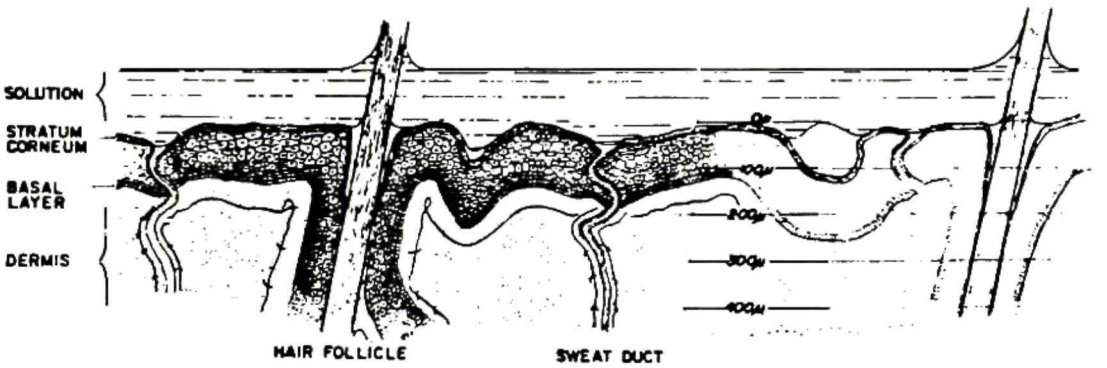

Figure I

Schematic diagram of the human skin showing the composite diffusion barrier and appendageal diffusion shunts. (adapted from Scheuplein and Blank)

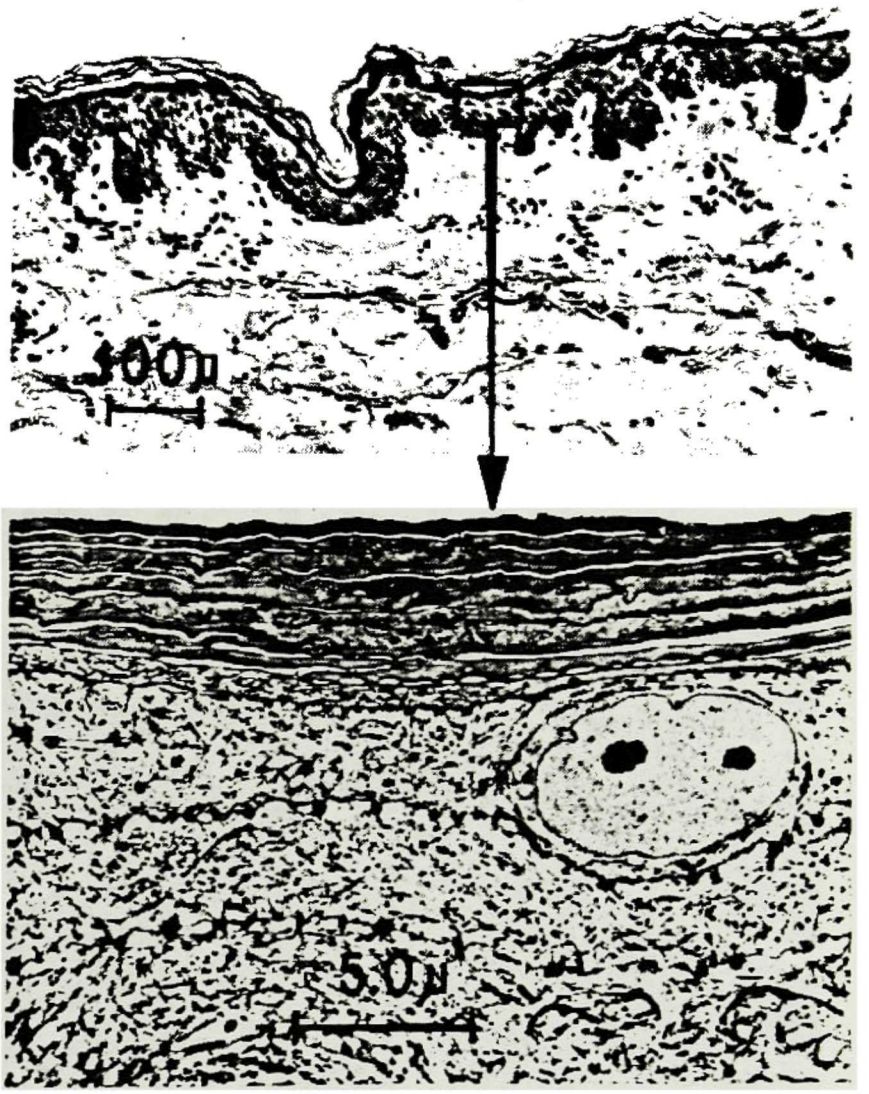

Figure 2

Top: Histological stained cross section of human skin. Note the porous appearance of the stratum corneum.

Bottom: Electron photomicrograph of the uppermost layer of the epidermis showing 10 cell layers of stratum corneum.

(adapted from Scheuplein and Blank)

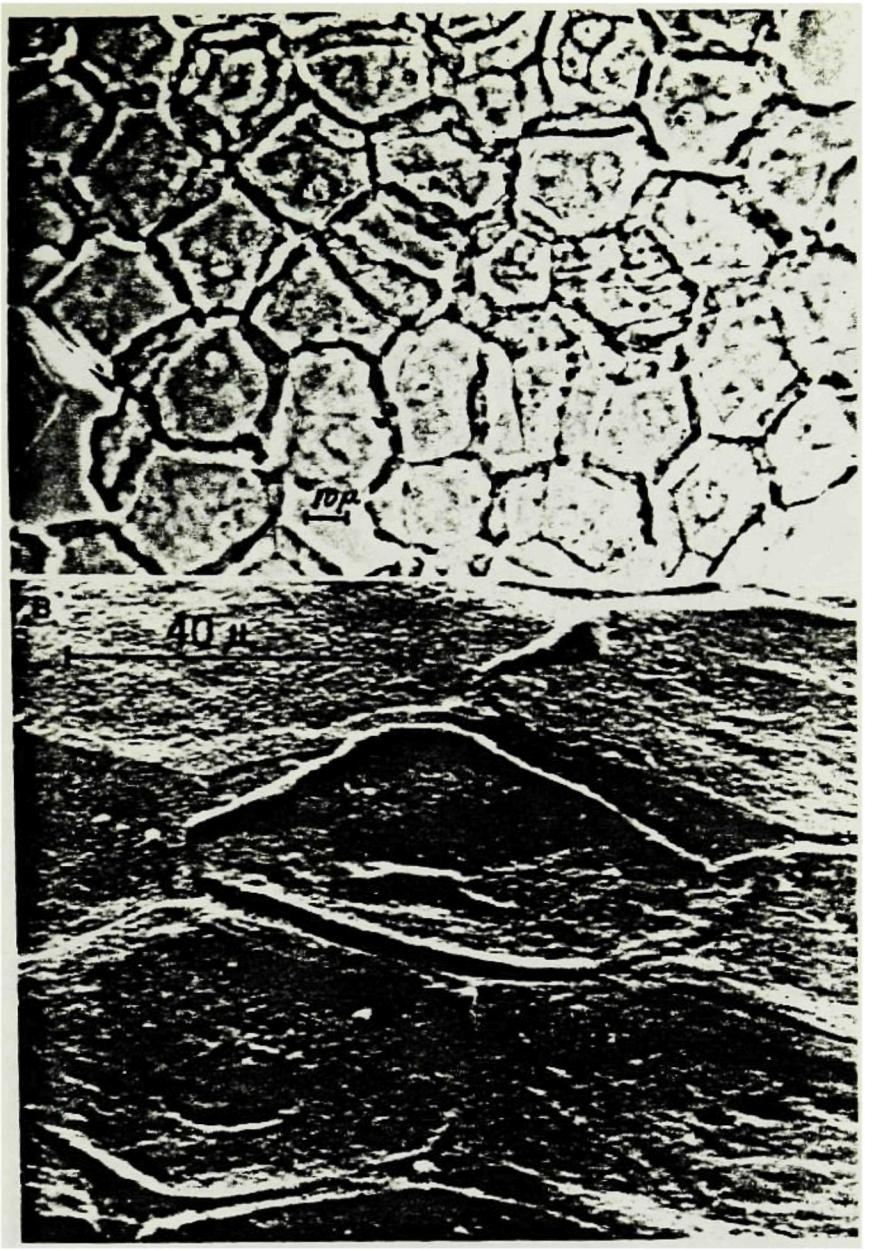

Figure 3

Top: Phase contrast micrograph of a representative "single cell layer" of the stratum corneum. The dark bands at the cell borders are regions of cell overlap.

Bottom: Scanning electron photomicrograph of the outer surface of the stratum corneum. Again, note the raised regions of cell overlap at the cell borders.

(adapted from Scheuplein and Blank)

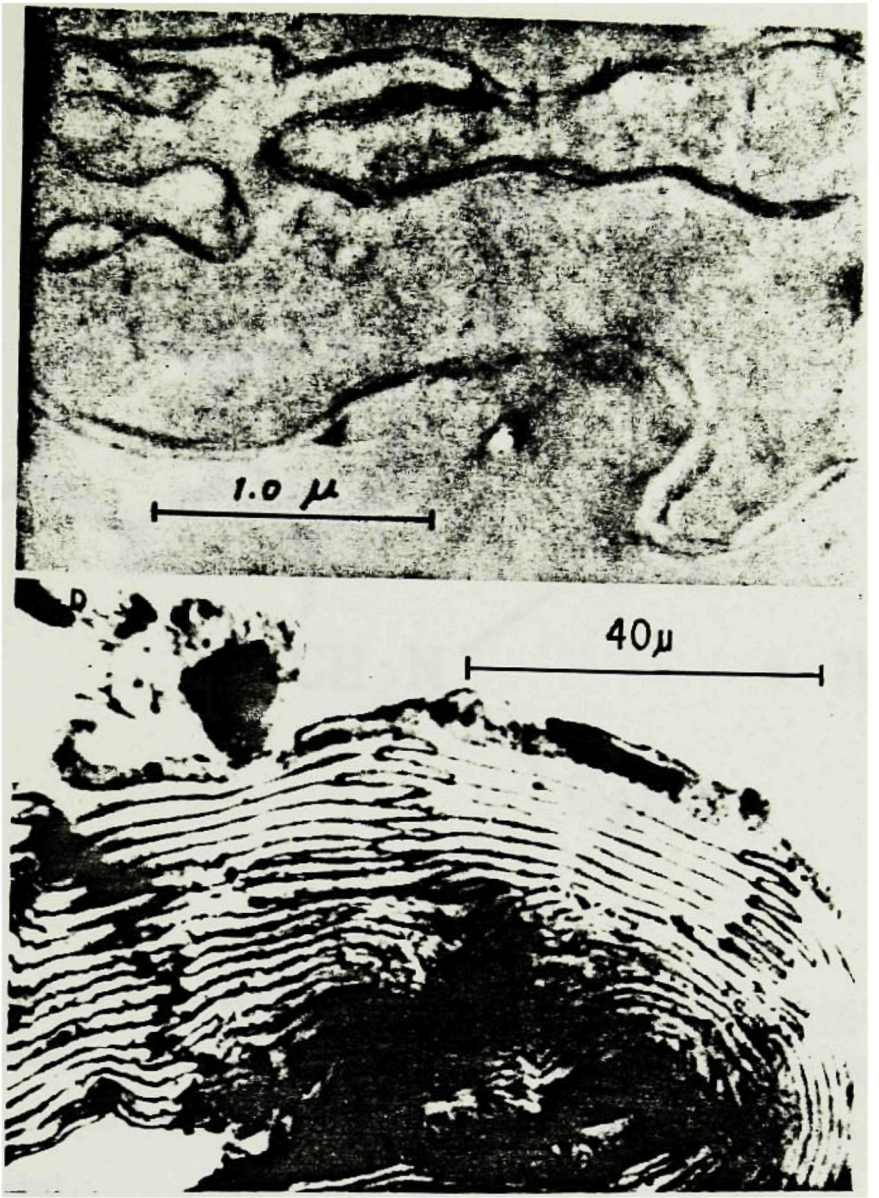

Figure 4

Top: Electron photomicrograph of filled intercellular regions in stratum corneum. Note the convolutions and interdigitations in adjacent cell boundaries.

Bottom: Stained cross section of stratum corneum. showing the stacking of cells.

(adapted from Scheuplein and Blank)

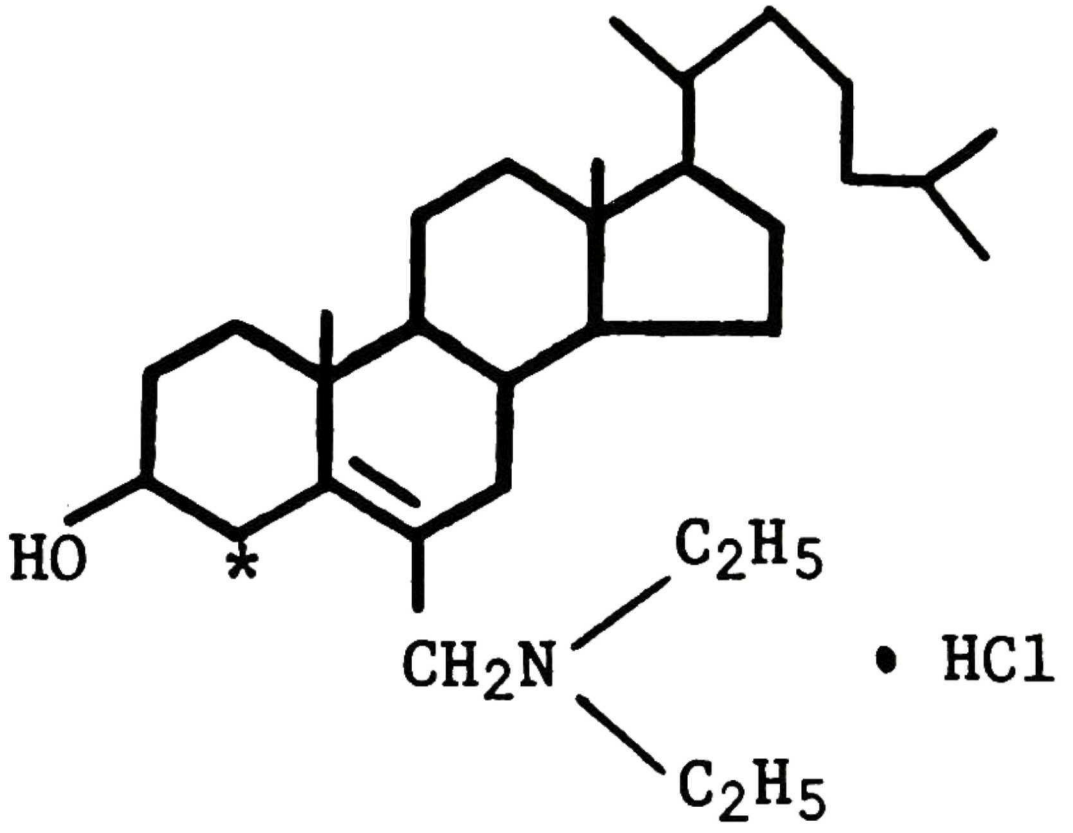

Figure 5

Structure of SC-23110 (6-diethylaminomethylcholest-5-ene-3-β-ol, hydrochloride), an experimental anti-acne agent administered intravenously and topically to Rhesus monkeys. The asterisk denotes the position of the ^{14}C label.

(adapted from Wester and Noonan)

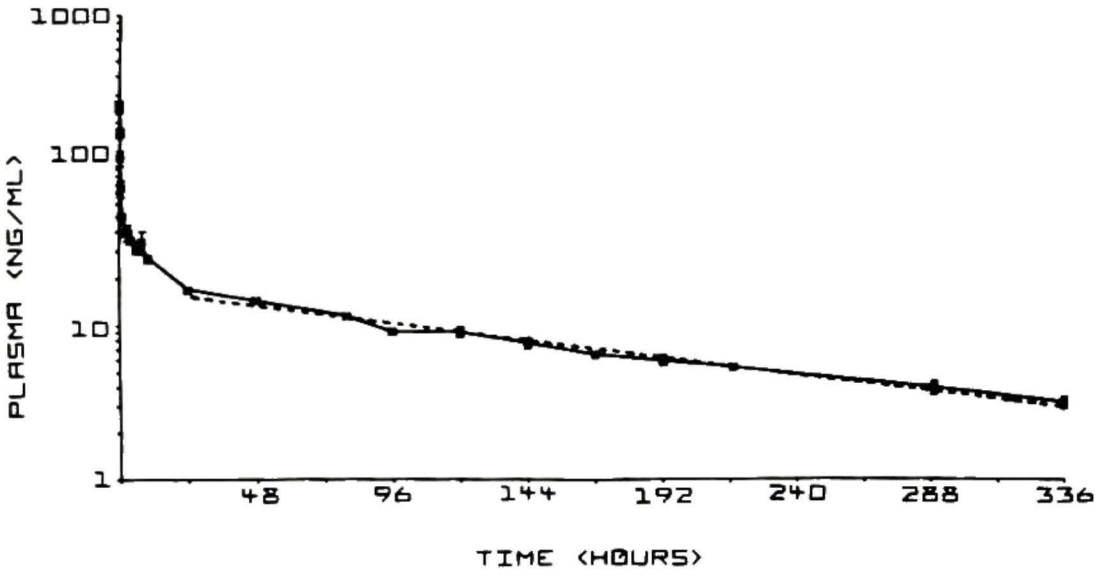

Figure 6

Plasma concentration vs. time curve of total radioactivity following intravenous administration of SC-23110. Units: ordinate; radioactivity, as ng equivalents per ml plasma assuming the same specific activity as SC-23110, abcissa; time, in hours. The dotted line is the linear regression line for 24 to 336 hours. Each point is expressed as the mean ± standard error for 3 monkeys. (adapted from Wester and Noonan)

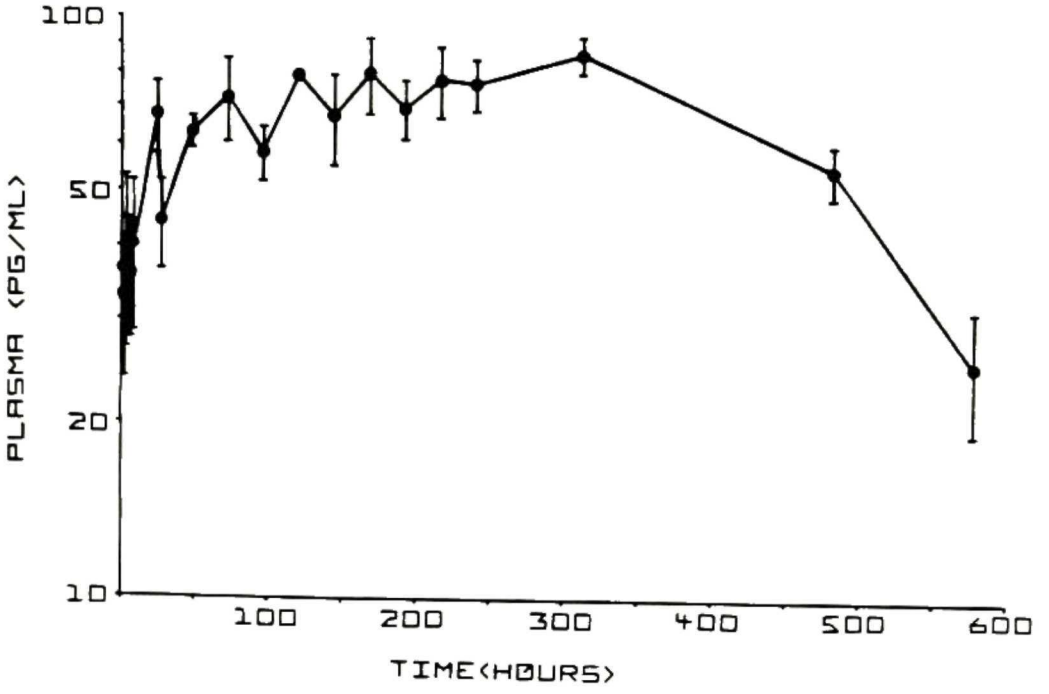

Figure 7

Plasma concentration vs. time curve of total radioactivity following topical administration of SC-23110, when applied as the free base. Units: ordinate; radioactivity, as pg equivalents per ml of plasma assuming the same specific activity as the free base form of SC-23110, abcissa; time, in hours. Each point is expressed as the mean ± standard error for 3 monkeys (48 and 120 hr. points are for 2 monkeys).

(adapted from Wester and Noonan)

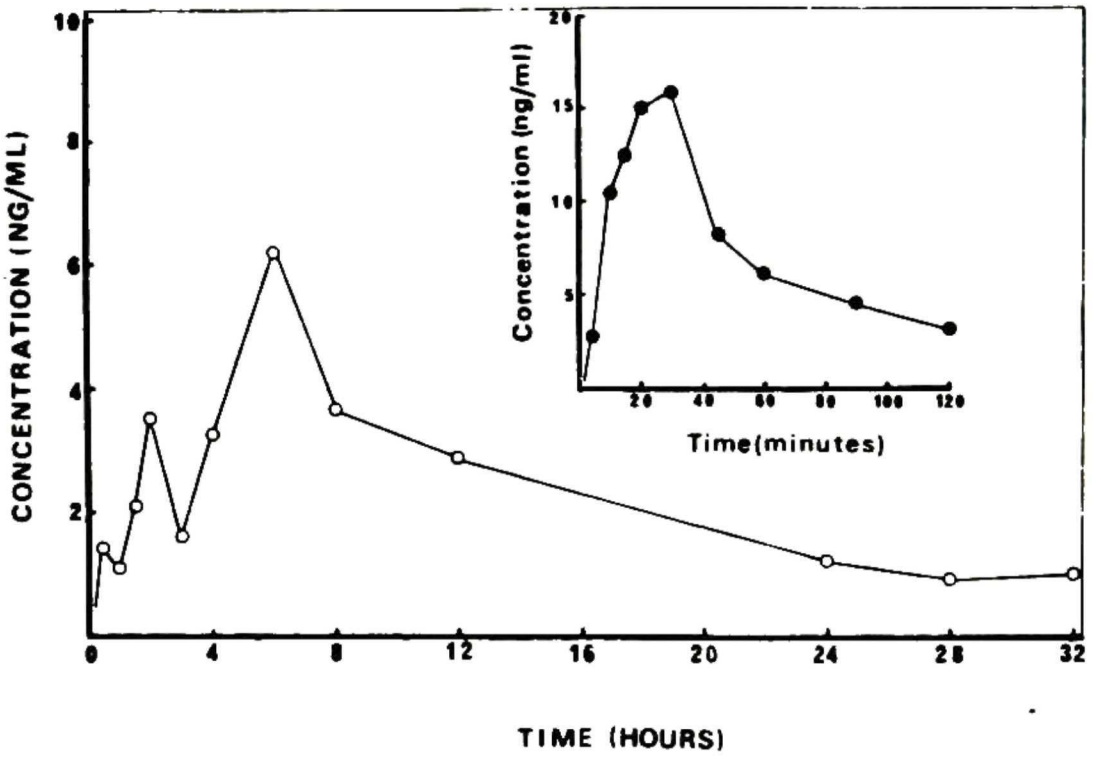

Figure 8

Mean plasma Isosorbide Dinitrate concentrations after sublingual administration (inset) and after topical application. Units: ordinate; concentration in ng/ml of plasma, abcissa; time, in hours. (adapted from Mansel-Jones et.al.)

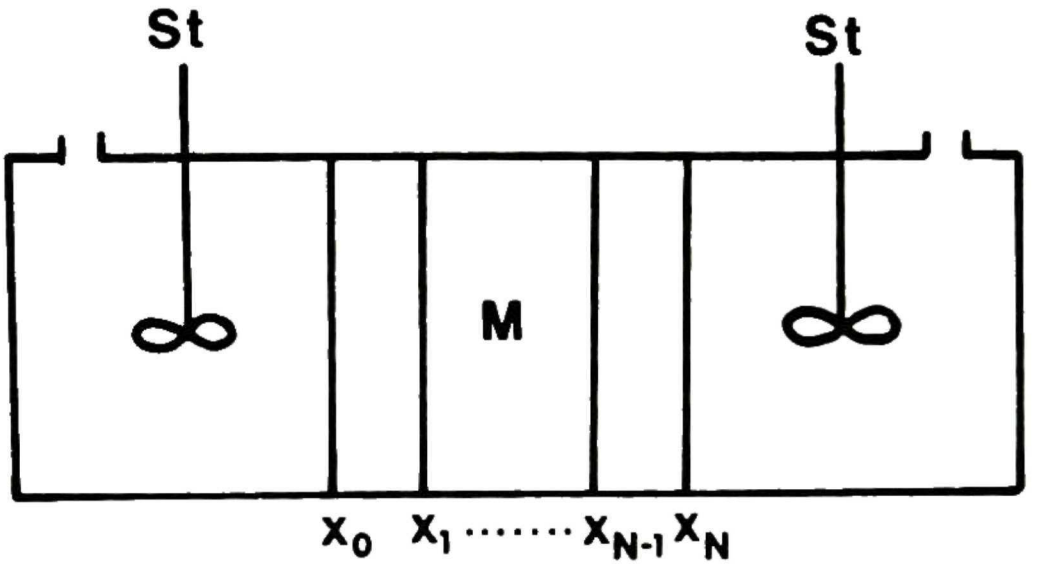

Figure 9

Multilayer schematic model for simultaneous diffusion and metabolism by the skin. Key: M, cutaneous membrane that consists of N layers; St, stirrers. Note that the inner and outer surfaces of the membrane are depicted as well-stirred compartments.

(adapted from Yu et.al.)

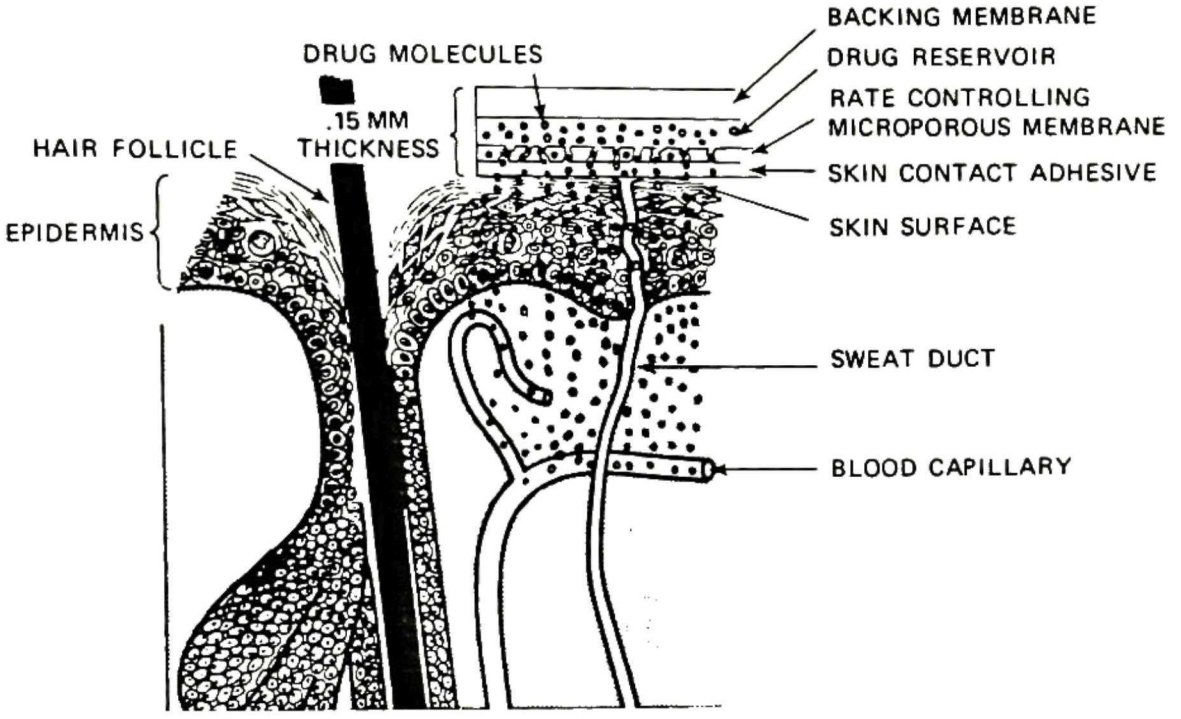

Figure 10

Schematic drawing of the Transdermal Therapeutic System in place on the surface of the skin.

(adapted from Shaw and Chanrasekaran)

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